REMARKS/ARGUMENTS

Claims 1-16 are presently under consideration. Claims 17-31 were previously canceled in response to a restriction requirement. This response amends claims 2, 3, and 16. Support for these amendments can be found throughout the specification and at least at page 15, lines 10-23. The paragraph numbering below follows that of the Office Action.

Specification

¶2. Applicant has amended certain portions of the specification to correct typographical errors. These amendments are similar to amendments made in the parent application. Applicant has also amended the specification to add a reference to the parent application. No new matter is introduced by these amendments.

¶3. Applicant has amended the specification at paragraphs 70, 71, 73, 75, 117, 118, 129, 134, 150, 151, and 163 to provide the patent number for application number 08/835,159 (now U.S. 6,555,310, issued April 29, 2003).

¶4. Applicant has amended the specification at paragraphs 74 and 79 to delete references to deposits.

Rejections Under 35 U.S.C. §112

¶5. Claim 7 was rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. According to the Action, the specification lacks complete deposit information for the deposit of hybridoma producing monoclonal antibodies SCPc.4.PC. Applicant has canceled claim 7. Withdrawal of this rejection is respectfully requested.

¶6. Claims 2, 3, and 16 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not in possession of the inventors. This rejection is traversed in part and overcome in part as follows.

According to the Office Action, Applicants were not in possession of PDI having at least ten consecutive amino acids of which are substantially identical to a subsequence of an amino acid sequence of SEQ ID NO:3 or PDI's that have an amino acid sequence that is

substantially identical to the amino acid sequence of SEQ ID NO:2. The Office Action asserts that the specification does not provide functional/structural characterization or isolation protocols for amino acid sequences having substantial identity to SEQ ID NOS:2 or 3.

Although Applicant traverses the rejection, to expedite prosecution of the instant application, Applicant has amended claims 2, 3, and 16 to recite a capture reagent that comprises an antibody that specifically binds to either amino acid sequence SEQ ID NOS: 2 or 3. Withdrawal of this rejection is respectfully requested.

¶7. Claims 2, 3, and 16 were rejected under 35 U.S.C. §112, second paragraph, for allegedly failing to particularly point out and distinctly claim the invention. This rejection is traversed in part and overcome in part as follows.

According to the Office Action, recitation of the term "substantially identical" renders the claims indefinite. Although Applicant traverses the rejection, to expedite prosecution of the instant application, as noted above, amended claims 2, 3, and 16 do not recite the term "substantially identical." Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §103

¶8. Claims 1, 3-6, and 8-15 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Anusz et al., Journal of Clinical Microbiology, 28(12):2770-2774 (1990) ["Anusz"] in view of Blunt et al., Gene, 181:221-223 (1996) ["Blunt"]. This rejection is respectfully traversed.

According to the Office Action, Anusz describes an ELISA assay for detection of *C. parvum* whole oocysts in bovine feces, and Blunt describes the sequence of a soluble protein disulfide isomerase (PDI) of *C. parvum*. While acknowledging that the Anusz fails to teach the use of a reagent which specifically binds to a protein disulfide isomerase of *C. parvum*, the Action nonetheless asserts that one would be motivated to combine Blunt and Anusz to produce the presently claimed methods and kits for diagnosing *Cryptosporidium* infection.

Anusz discusses an assay which employed antibodies against *C. parvum* oocysts to detect *C. parvum* oocysts in stool. However, PDI is a soluble protein not expected to be

present in stool. Therefore, it would not have been obvious for one to employ an antibody against PDI in the whole oocyst diagnostic method.

Applicants present the following remarks and evidence to further demonstrate that the presently claimed invention would by no means have been obvious over the cited art.

A. Expert declaration regarding the cited art

Applicants submit herewith a Declaration of Dr. Gunars E. Valkirs, a coinventor of the subject invention and also an expert in the field of development and testing of immunodiagnostic assays. This Declaration was previously submitted in the parent case, U.S. Patent Application No. 09/158,180. The parent case contained kit claims which were configured to perform methods similar to those presently claimed in the instant application. The comments provided by the Declaration are therefore similarly applicable to the presently claimed methods and kits.

In his declaration, Dr. Valkirs points out that conventional methods for diagnosis of crytosporidiosis relate to detection of oocyst surface-antigens (see also the discussion of Anusz at page 2770, third full paragraph, citing 28 references) and that Anusz discusses just one example of such methods. Dr. Valkirs explains that proteases are abundant in stool and would be expected to degrade a soluble antigen such as PDI. Therefore, Dr. Valkirs notes that PDI was not known to be present in stool and that soluble antigens were not expected to be viable targets for detecting *C. parvum* infection.

As for Blunt, Dr. Valkirs points out that this reference merely reports that under laboratory conditions an antiserum against *C. parvum* binds to cells harboring *C. parvum* genomic DNA and that one of the cells comprises a putative C. parvum PDI sequence. It is to be noted that the antiserum used in Blunt is raised against a homogenate of purified *C. parvum* oocysts and sporozoites rather than a soluble PDI antigen. Dr. Valkirs notes that Blunt does not even remotely suggest that PDI is present in stool or that antibodies against a soluble antigen PDI (or any other *C. parvum* antigen) can be used in a diagnostic assay for detecting Cryptosporidium in stool. Dr. Valkirs further explains that the essence of the Blunt data is that *C. parvum* may express a specific antigen (i.e., PDI) rather than any implication on how to diagnose *C. parvum*.

In the last sentence of paragraph 6 of the Declaration, Dr. Valkirs expresses his opinion that the identification of *C. parvum* PDI would not make it obvious that the prevalent oocyst surface antigen-based methods (e.g. Anusz et al.) should be modified by detecting a soluble antigen such as PDI in stool. Dr. Valkirs notes that it is one thing to know that *C. parvum* express PDI, but quite another to suggest that a soluble antigen such PDI is present in stool and suitable for detection with an antibody against PDI. Dr. Valkirs further explains that just like many other soluble antigens that are known to be expressed by *C. parvum*, the identification of an additional soluble antigen of *C. parvum* (i.e., PDI) provides no suggestion or motivation to modify the prevalent oocyte-based methods (e.g., the Anusz assay).

As indicated in Dr. Valkirs' declaration, Dr. Valkirs has extensive experience in the development of various unique immunoassays for the detection of microorganism infections. It is submitted that Dr. Valkirs' stature as an expert in the field merits appropriate deference. "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Guidelines for Examination of Applications for Compliance with the Utility Requirement at §B4. Appropriate deference by an Examiner to the opinion of an expert is also emphasized by *In re Soni* which holds that the opinion of an expert must be accepted "in the absence of evidence to the contrary." 34 USPQ2d 1684, 1688 (Fed. Cir. 1995).

B. No motivation or suggestion to combine the cited references

As illustrated by Dr. Valkirs, the cited references provides neither a motivation to combine art teachings nor a reasonable expectation of success for one to combine the cited references to practice the presently claimed invention. The Examiner is asked to step back in time without hindsight from the subject application. The question, then, that needs to be asked is whether an ordinarily skilled artisan, in view of the availability of methods of detecting Cryptosporidium oocysts in stool and the well known knowledge that stool is high in proteases, would nonetheless have been motivated to develop a new assay for diagnosing *Cryptosporidium*

with a reasonable expectation that *Cryptosporidium* infection could be diagnosed by detecting a soluble antigen such as PDI in stool.

As discussed above, Anusz provides no suggestion or motivation for detecting a soluble antigen such as PDI in stool. And at most, Blunt demonstrates the ability of an antiserum raised against a crude *C. parvum* preparation to bind to a lysed PDI-expressing colony under laboratory conditions. This provides no reason to expect that *C. parvum* PDI is present and can be detected with an antibody in a crude sample such as stool or other biological samples from a potentially infected patient. Nor was there any teaching in the cited references that a soluble antigen-based detection scheme would be advantageous over the oocyst-based method. Further, in view of the abundance of proteases in stool, one is likely to be discouraged to attempt a soluble antigen-based method for detecting *Cryptosporidium* in stool. One would certainly not have had a reasonable expectation that such a method would actually work.

Thus, the answer to the above-hypothesized question would be undoubtedly in the negative. Applicants further submit that any motivation to combine the cited references, as alleged in the Office Action, would have come only from the subject application rather than the cited references themselves. Therefore, it is submitted that no *prima facie* case has been or could be established to maintain the instant obviousness rejection.

C. The Office Action merely recites conclusory statements of obviousness

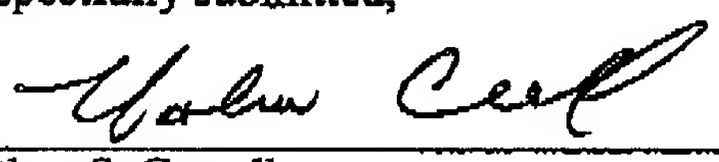
Applicants note that no concrete reasoning or evidence was set forth in the Office Action to support the alleged motivation or suggestion to combine teachings of the cited references. The statement in the Office Action that one would have been motivated to combine the description of PDI in Blunt with the method discussed in Anusz is conclusory and appears to be based on improper hindsight gleaned from Applicants' disclosure rather than the cited references. It is noted that a finding of *prima facie* obviousness requires "rigorous application of the requirement for a showing of a teaching or motivation to combine prior art references." In re Dembiczak, 175 F.3d 994, 999 (1999). The showing of obviousness requires actual evidence that is clear and particular. Id. The Federal Circuit has made it clear that "broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence'" Id.

Applicants submit that such is not the standard that has been applied by the Office in maintaining the instant rejection.

In summary, the presently claimed invention would by no means have been obvious because there would have been no suggestion or motivation to combine teachings of the cited references. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Nathan S. Cassell
Reg. No. 42,396

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400 / Fax: 415-576-0300

Attachment - *Copy of Declaration of Dr. Gunars E. Valkirs of 09/26/01*

NSC:nap
60256319 v1